ORIGINAL ARTICLE

Biliary Cysts in Children — Long-term Follow-up in Taiwan

Hung-Chang Lee,[1,2] Chun-Yan Yeung,[1] Shiuh-Bin Fang,[1,3] Chuen-Bin Jiang,[1] Jin-Cherng Sheu,[4] Nien-Lu Wang[4]*

Background: This study analyzed the clinical presentation, postoperative morbidity and mortality and incidence of associated extrahepatic biliary atresia in children with biliary cysts in Taiwan.

Methods: We retrospectively reviewed the records of 158 pediatric patients with biliary cysts seen between June 1981 and July 2004, with follow-up ranging from 12 months to 22 years (mean, 11.2 ± 6.1 years). Patients were divided into three groups: biliary atresia-associated biliary cyst (BABC, 21 patients), non-biliary atresia-associated choledochal cyst (NBACC) in infancy (37 patients), and late NBACC (> 1 year of age, 100 patients).

Results: BABC accounted for 36.2% of the infantile biliary cysts in this study. Extrahepatic cysts in late NBACC had a greater mean diameter than those in infantile NBACC and BABC (21.5 mm vs. 16.0 mm vs. 7.9 mm, $p < 0.001$). Cholangitis was the most serious complication within 3 months postoperatively in all three groups, resulting in four deaths (two in the infantile NBACC group and one each in the other two groups). Liver cirrhosis developed during long-term follow-up in nine of the 21 patients with BABC, four of whom died. Three of these nine patients underwent liver transplantation and remained well during follow-up. Chronic complications in NBACC occurred mainly in late IVa cases, with persistent intrahepatic dilatation developing in 12 of 35 patients and intrahepatic stones in five. Elevation of serum alanine aminotransferase (ALT) was found preoperatively in 85% of late NBACC and 35% of infantile NBACC cases. Postoperative normalization of ALT occurred after a mean of 152 ± 23 days and 158 ± 67 days in late NBACC and infantile NBACC, respectively. Higher ALT levels before operation were associated with a longer period until normalization.

Conclusion: The possibility of BABC must be included in the differential diagnosis when a small extrahepatic cyst (< 8 mm in diameter) with prolonged jaundice is found in infancy. Postoperative follow-up is essential for patients with NBACC due to their frequently prolonged elevation of serum ALT and possibility of residual intrahepatic dilatation. Cholangitis was the major cause of death within 3 months postoperatively in this study. [*J Formos Med Assoc* 2006;105(2):118–124]

Key Words: biliary atresia, biliary cyst, biliary atresia-associated biliary cyst, non-biliary atresia-associated choledochal cyst

Cystic malformation in the biliary tree is an uncommon anomaly in Western populations but comparatively frequent in Asian children.[1–7] The etiology is still controversial.[8] It is often located in the common bile duct (choledochus), and is thus referred to as choledochal cyst.[9] Alonso-Lej and associates[10] classified extrahepatic biliary cysts into three types based on anatomic characteristics, and Todani et al[11] added two more types into the classification.

Previous studies reported that extrahepatic biliary atresia (BA) might be associated with biliary

[1]Department of Pediatrics, Mackay Memorial Hospital, [2]Department of Pediatrics, Taipei Medical University, [3]Department of Pediatrics, Taiwan Adventist Hospital, and [4]Department of Pediatric Surgery, Mackay Memorial Hospital, Taipei, Taiwan, R.O.C.

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***Correspondence to:** Dr. Hung-Chang Lee, Department of Pediatrics, Mackay Memorial Hospital, 92, Section 2, Chung Shan North Road, Taipei 104, Taiwan, R.O.C.
E-mail: ped2435@ms2.mmh.org.tw

cysts (BC).[12,13] Komuro et al observed that 20% of BA patients had extrahepatic BC.[14] However, few studies have looked at the converse question, that is, the incidence of BA in patients with BC. We retrospectively analyzed the clinical presentation, postoperative morbidity and mortality and the incidence of associated BA in 158 cases of pediatric BC diagnosed over a 23-year period.

Methods

Biliary cysts were diagnosed based on history, physical examination, biochemical and imaging studies in 173 patients (age range, 2 days to 16 years) between July 1981 and June 2004. Patients with intrahepatic cysts due to complications after Kasai operation for BA, patients operated on elsewhere, and those followed up for less than 12 months (except when due to death) were excluded. The remaining 158 patients who were included in this study all had a definitive surgical diagnosis of BC. Operative cholangiograms were done in most cases, and magnetic resonance cholangiopancreatograms (MRCP) in selected cases. Pathology reports of surgical specimens were available for all patients. This study was approved by the hospitals' institutional review boards.

We defined the following groups for analysis: BA-associated BC (BABC) and non-BA-associated choledochal cyst (NBACC). The latter group was subdivided into infantile and late (> 1 year old) groups to enable comparison of infants in the BABC and NBACC groups. The cysts in the NBACC group were categorized according to the five types in Todani et al's classification.[11] The three main types of BA were defined based on the classification system used by the Japanese Society of Pediatric Surgeons.[15]

Biochemistry studies, including serum alanine aminotransferase (ALT), were done for all patients just before operation. Scheduled follow-up evaluations in the outpatient clinic included biochemistry and abdominal sonogram at 4-week intervals for 3 months postoperatively and every 3–12 months thereafter. Serum ALT greater than 40 U/L was defined as elevated. Subsequent normalization of ALT was defined as two normal values reported 1–3 months apart. Serum amylase above 120 U/L was defined as elevated. Data recorded from the charts through the clinical course included clinical manifestations, results of diagnostic studies, postoperative complications, morbidity and mortality. Chi-square test, ANOVA or two-tailed F test was used as appropriate for comparison of differences between the groups and to analyze correlations between variables. Statistical significance was defined as a p value of less than 0.05.

Results

Among the 158 cases of BC included, 21were classified as BABC, 37 as infantile NBACC, and 100 as late NBACC. The duration of follow-up ranged from 12 months to 22 years (mean, 11.2 ± 6.1 years). The most commonly performed operations were Kasai operation for BABC, and radical cyst excision with hepaticojejunostomy for NBACC (except for type V, in which lobectomy was the most common procedure). The age and gender of patients and anatomic classification of the cysts are summarized in Table 1. There was a female predominance in all three groups. The 21 patients with BABC were all infants and accounted for 36.2% (21/58) of those with infantile BC. The age at diagnosis of NBACC gradually decreased over the study period (r = 0.25, p = 0.002) (Figure 1).

The most common type of NBACC in both the infantile and late groups was type I (97.2% and 62%, respectively), followed by type IVa (1.6% and 35%, respectively). Of the 21 BABC cases, 19 had type I BA with extrahepatic cysts, one had type III BA with a left intrahepatic cyst, and one had type III BA with a cyst at the cystic duct. The patient with type III BA associated with an intrahepatic cyst was a 2-month-old boy who had a cyst in the left liver which persisted after Kasai operation. He developed portal hypertension with recurrent bleeding from esophageal varices 2 years

Table 1. Gender and anatomic classification of 158 cases of biliary cysts

	BABC (n = 21)	Infantile NBACC (n = 37)	Late NBACC (n = 100)	Total
Age	2.4 ± 1.5 mo	5 ± 2.5 mo	4.6 ± 2.8 yr	
Gender, *n*				
Male	9	14	35	58
Female	12	23	65	100
Classification*, *n*				
Ia	19	27	48	94
Ic	0	3	14	17
II or III	0	0	0	0
IVa	0	6	35	41
V	1	1	3	5
Unclassified, *n*	1	0	0	1

**According to Todani et al's classification.[11] BABC = biliary atresia-associated biliary cyst; NBACC = non-biliary atresia-associated choledochal cyst.*

later and underwent liver transplantation at 8 years of age. The other patient with type III BA was a 3-month-old girl who had a cyst at the cystic duct; despite undergoing Kasai operation, she developed portal hypertension and intractable bleeding from esophageal varices at 6 months of age. At 11 months, she received a liver transplantation. Both of these patients have remained well over a follow-up period of 11 and 4 years, respectively.

The symptoms and signs in the three groups of patients are listed in Table 2. Four patients with infantile NBACC diagnosed by prenatal sonogram had no clinical symptoms preoperatively. In infancy, the most common presenting sign was jaundice (all 21 patients with BACC and 33 of 37 with infantile NBACC). Abdominal pain was the most common symptom in late NBACC, with vomiting being the second most common. In patients with late NBACC, the classic triad of abdominal pain, jaundice and right upper abdominal mass was present in only 9% (9/100).

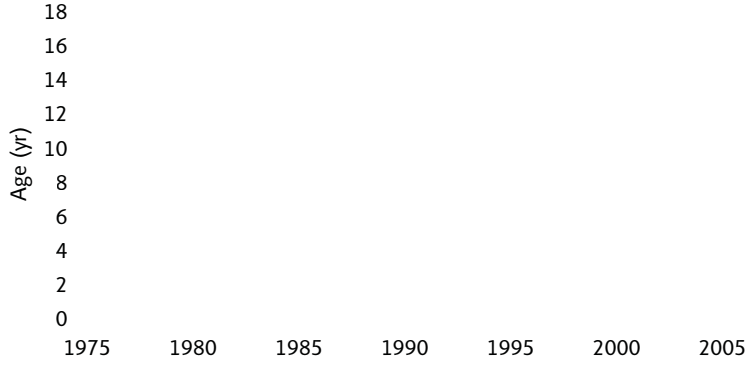

Figure 1. Age at diagnosis of non-biliary atresia-associated choledochal cyst decreased over the study period (r = 0.25, p = 0.002).

The diameter of the extrahepatic bile duct was measured sonographically for each patient who had extrahepatic biliary cysts. The mean diameter in BABC (7.9 ± 1.5 mm) was significantly less than that in infantile NBACC (16.0 ± 3.7mm, $p < 0.001$) and late NBACC (21.5 ± 5.6 mm, $p < 0.001$). In NBACC, older age at diagnosis was associated with greater cyst diameter ($r = 0.7$, $p < 0.001$). Association with biliary hypoplasia of the common bile duct (CBD) was found in one of the 37 cases of infantile NBACC. One patient with BABC had jaundice and acholic stool at 2 months of age, but no cyst was found on sonogram at that time; BA was suspected after a series of examinations including sonography and hepatobiliary nuclear medicine scan. The family refused operation and he was lost to follow-up. However, he was brought back to our hospital at 9 months of age due to persistent jaundice and clay-colored stool. Sonographic examination revealed a cyst (5 mm in diameter) in the portal area. A Kasai procedure was performed and revealed a cyst followed by an extremely narrowed CBD lumen. The patient died of liver cirrhosis and hepatic failure 1 month after the procedure.

Table 2. Clinical presentation of 158 patients with biliary cysts

	BABC (*n* = 21)	Infantile NBACC (*n* = 37)	Late NBACC (*n* = 100)
Acholic stool, *n*	21	27	7
Prolonged jaundice, *n*	21	7	0
Periodic jaundice, *n*	0	26	20
Abdominal pain, *n*	0	4	72
Vomiting, *n*	0	5	72
Fever, *n*	0	6	17
Mass, *n*	0	0	15
Classic triad, *n*	0	0	9
Asymptomatic, *n*	0	4	0

BABC = biliary atresia-associated biliary cyst; NBACC = non-biliary atresia-associated choledochal cyst.

Stones in the gallbladder or CBD were found before operation in 13% of late NBACC cases, but in no infantile NBACC or BABC cases. Postoperative intrahepatic stones were found in five of 35 type IVa late NBACC. Postoperative complications within 3 months included adhesive ileus presenting as intestinal obstruction with bilious vomiting in 6 patients, ascites in 15, subphrenic fluid collection in four, episodes of cholangitis in 18, and sepsis in eight. Of the 18 patients with cholangitis, eight had BABC, six had infantile NBACC, and four had late NBACC. Four children died as a result of these conditions, two with infantile NBACC and one each in the other two groups.

Chronic postoperative complications in NBACC included adhesive ileus in four patients, intrahepatic stones in five, intrahepatic cysts in 12, and portal hypertension with bleeding esophageal varices in one. Liver cirrhosis developed in nine patients in the BABC group, of whom four died and three underwent liver transplantation (Table 3). No patients with NBACC died later than 3 months postoperatively except for one who had spinal muscular dystrophy and died suddenly at 11 years of age.

Postoperative intrahepatic cysts were found in the portal area in 12 of the 35 patients with type IVa NBACC, and five of these 12 had intrahe-

Table 3. Postoperative complications of biliary cysts

	BABC (*n* = 21)	Infantile NBACC (*n* = 37)	Late NBACC (*n* = 100)
Acute complications (< 3 mo), *n*			
Adhesive ileus	2	0	4
Ascites	1	4	10
Subphrenic abscess	0	0	4
Cholangitis	8	6	4
Sepsis	4	2	2
Death due to infection	1	2	1
Death due to liver failure	1	0	0
Late complications (> 3 mo), *n*			
Adhesive ileus	0	0	4
Intrahepatic cyst	0	0	12
Intrahepatic stone	0	0	5
Liver cirrhosis/portal hypertension	9	0	1
Death	4	0	0

BABC = biliary atresia-associated biliary cyst; NBACC = non-biliary atresia-associated choledochal cyst.

patic stones. Three of these patients developed intermittent abdominal pain and jaundice several months later, and two of them underwent surgical revision. The third patient who did not undergo a repeat operation developed portal hypertension with esophageal varices 8 years later. Portal hypertension eventually developed in nine of 21 patients with BABC, compared with only one of 137 with NBACC ($p < 0.001$).

Serum amylase (282 ± 134 U/L) was elevated in 70 of the 98 patients with NBACC in whom it was tested, but the values in all patients returned to normal 1 month after operation. Elevated serum ALT was found before operation in 85 of 100 patients with late NBACC (184 ± 22 U/L), 13 of 37 with infantile NBACC (109 ± 61 U/L), and 17 of 21 with BABC (115 ± 62 U/L). Of the 137 patients with NBACC, 101 had normal ALT within 1 year after operation (48 in 1 month, 33 in 1–3 months, and 20 in 4–12 months) compared with only two in the BABC group ($p < 0.001$). ALT normalized after a mean of 152 ± 23 days in late NBACC and 158 ± 67 days in infantile NBACC. No correlation between age and preoperative serum ALT level ($r = 0.11$, $p = 0.3$) was found in patients with NBACC, but a higher ALT level before operation was associated with a longer duration until normalization ($r = 0.47$, $p < 0.001$) (Figure 2). No pancreatitis or malignancy was detected during follow-up.

Discussion

The etiology of BC remains unknown.[9,15–18] The recommended treatment for extrahepatic BC has been radical cyst excision with a Roux-en-Y hepaticojejunostomy as the primary procedure.[3,4,19,20] However, when BA is associated with a CBD cyst (type I cyst), a Kasai operation is the treatment of choice.[21,22] A previous study reported that BC was mostly associated with type I BA.[14] In this study, BA was found in 36.2% of infants with BC, with 19 of 21 patients having type I BA. The fact that one patient with BABC (type I BA) did not have a cyst identified sonographically on initial evaluation suggests that the BC in this case may have been secondary to distal obstruction of the CBD rather than being congenital.

Stringer et al reported that among 78 patients with choledochal cyst seen over 20 years, 69% presented with jaundice associated with abdominal pain and 18% with abdominal pain alone.[3] In this series, late NBACC most commonly presented with abdominal pain (72%), which was associated with jaundice in 20% of cases. Although vomiting has seldom been reported as a manifestation of BC, it was found in 72% of our patients with late NBACC. Only 9% of patients with late NBACC had the classic triad of abdominal pain, jaundice and abdominal mass. The decreasing age at diagnosis for NBACC over the course of this study period

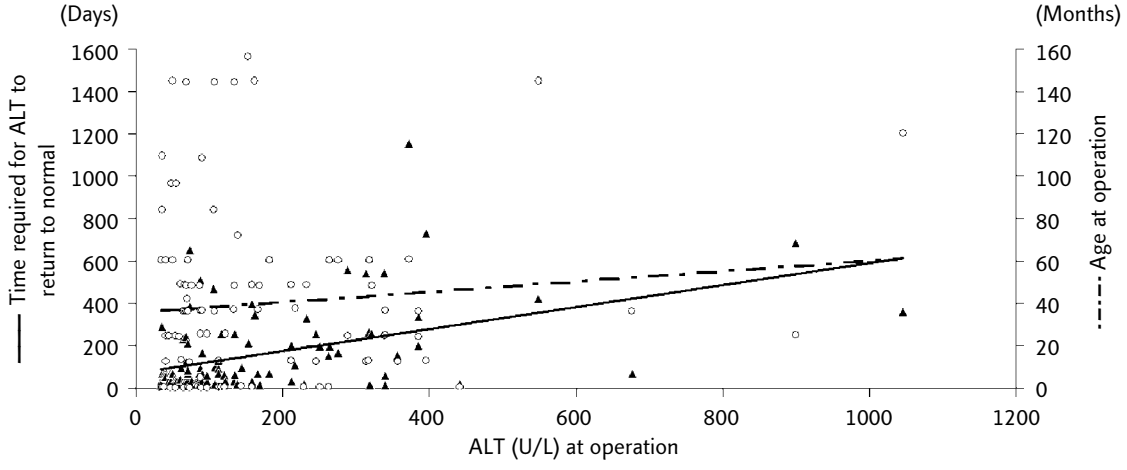

Figure 2. Serum alanine aminotransferase (ALT) level: age at operation and time required for serum ALT to return to normal after operation.

suggests that earlier diagnosis did not allow enough time for development of the classic triad.

In this study, jaundice was the most common presenting sign of BC in infancy, in both the BABC (100%) and NBACC (89%) groups. However, all patients with BABC had acholic stool together with jaundice, compared with only 27 of 33 patients with jaundice in the infantile NBACC group ($p = 0.03$), indicating that infantile BABC is more likely to cause complete biliary obstruction than NBACC.

Although new tools such as MRCP have become available for the diagnosis of BC,[9,23,24] sonography remains the most useful imaging modality.[3,25–27] In our previous study, sonography had a specificity of 97%.[27] In this study, the cysts in patients with NBACC were of significantly greater diameter than patients with BABC, suggesting that BABC must be considered when a BC discovered in infancy is small (< 8 mm in diameter). Although the diameter of extrahepatic cysts correlated positively with age at diagnosis, we found no correlation between age and preoperative ALT level.

The prolonged period of ALT elevation prior to normalization in patients with BABC indicate the need for long-term follow-up in these patients. Ongoing hepatocellular injury, as indicated by persistently elevated ALT during follow-up, was also found in 85% of late NBACC and 35% of infantile NBACC patients, requiring a mean of 152 and 158 days to return to normal, respectively. Higher initial ALT was associated with a longer postoperative duration until normalization.

Although the prognosis of BC is excellent if radical excision is performed,[3–9] serious postoperative complications have been reported, including cholangitis, biliary stricture, intrahepatic biliary stones and portal hypertension.[28–34] Postoperative sonographic follow-up is equally important for both BABC and NBACC, especially for patients with type IVa NBACC, who are more likely to develop intrahepatic biliary cysts postoperatively. The most serious complication of NBACC in our series was portal hypertension with esophageal varices.

In our series, cholangitis was the most serious acute complication within 3 months postoperatively in each group, resulting in the death of four patients. Empiric antibiotics may be indicated in patients with biliary cysts who develop fever and jaundice within 3 months postoperatively.

In conclusion, BC in infancy must be evaluated carefully for the presence of associated BA due to the different surgical treatments and worse prognosis in these patients. Prolonged jaundice with acholic stool and a small cyst (< 8 mm in diameter) suggests the possibility of BABC. Although NBACC is generally benign, follow-up is necessary, especially for patients with late type IVa or elevated serum ALT before operation. In this study, postoperative cholangitis within 3 months of operation was the major cause of death.

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